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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,068	02/26/2002	Christopher H. Evans	018484-002121US	3205

7590 06/06/2005

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,068	EVANS ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-157* is/are pending in the application.

4a) Of the above claim(s) *1-142* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *143-157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/26/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 4/25/2005. Claims 1-157 are pending in the instant application. Applicants elected the subject matter of group V, drawn to claims 143-157, adenovirus as the species of vector and IL-10 as the species of DNA sequences encoding a biologically active gene product, with traverse. Further, applicants elected juvenile rheumatoid arthritis as the species of connective tissue diseases or disorders to unelected group III.

Applicant's election with traverse of the election requirement in the reply filed on 4/25/2005 is acknowledged. The traversal is on the ground(s) several grounds, addressed below. These arguments are not found persuasive.

Applicant argues that all of the claims in the instant application are directed to methods of therapeutic or prophylactic treatment of connective tissue diseases and that all of the claims revolve around the concept of using a nucleic acid sequence encoding gene products, which address one or more of the inflammatory, hypertrophic and erosive components of the disease or combat one or more of these pathological signs. Further applicant argues that the claims are linked together to form a single invention. As set forth in the previous office action each group is drawn to patently distinctive subject matter that encompasses methods of treating different diseases, using different vectors, a cell or inhibiting IL-1 biological responses. Each invention is patentably distinct from each other because they can either be used in different methods than each other or use different components from each other.

Applicant traverses the election of species requirement for a single vector, arguing that it is not reasonable to divide all of the vector sequences into individual species since

they can all be used in the claimed invention. An election of a single species from the genus of sequences is appropriate because: 1) the vectors have different sequences and modes of function; and 2) the heavy search burden on the examiner to search all of the listed vectors.

Further, applicant traverses the election of species requirement for a single biologically gene product, arguing that it is not reasonable to divide all of the nucleic acid sequences into individual species since they can all be used in the claimed invention. An election of a single species from the genus of sequences is appropriate because: 1) the nucleic acids have different sequences and encode proteins with different structures; and 2) the heavy search burden on the examiner to search all of the listed species.

Finally, applicant traverses the election of species requirement for a group III to a single connective tissue disease, arguing that it is not reasonable to divide all of the connective tissue diseases into individual species since they can all be treated in the claimed invention. An election of a single species from the genus of sequences is appropriate because: 1) the connective tissue diseases involve different tissues and have different pathologies and symptoms; and 2) the heavy search burden on the examiner to search all of the listed connective tissue diseases.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-142, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/25/2005.

Claims 143-157 are under consideration.

Specification

Applicant has filed two specifications, the first on 2/26/2002 and the second on 8/12/2002. Applicant has also filed amendments to the specification. However, since applicant has not explicitly indicated that the second specification replaces the first specification it is unclear which specification is to be amended. Applicant is reminded that any replacements or amendments to the specification must not introduce new matter. Applicant is requested to clearly indicate which specification is under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 143-157 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 143-157 are drawn to drawn to any polynucleotide, including a CDNA, RNA or genomic sequence, encoding any IL-10 cytokine from any species, wherein the IL-10 may be any biologically active fragment thereof. The claims encompass a genus of polynucleotides that are defined solely by the fact that they encode any IL-10 cytokine or

biologically active fragment thereof.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The claimed genus contemplated in the specification encompasses a nucleic acid sequence encoding any IL-10 cytokine or a biologically active fragment thereof (pg. 26, lines 17-22).

The factors to be considered when assessing possession of the claimed invention include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claims is the requirement that the polynucleotide encode any IL-10 cytokine or a biologically active fragment thereof. The specification does not contemplate using a specific IL-10 sequence. Nor does the specification describe what motifs or domains of an IL-10 cytokine must be conserved in the biologically active fragment or present in the IL-10 cytokine from any species in order to inhibit an IL-1 induced biological response.

Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of polynucleotides that are defined solely by the fact that they encode any IL-10 cytokine or biologically active fragment thereof.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written

Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for any genus of polynucleotides that are defined solely by the fact that they encode any IL-10 cytokine or biologically active fragment thereof. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 143-157 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide an enabling disclosure for a method of inhibiting any IL-1 induced biological response in any mammal by administering, by any route, any polynucleotide encoding IL-10.

The claims encompass a method of inhibiting any IL-1 induced biological response in any mammal by administering via any route, including *ex vivo*, any polynucleotide encoding IL-10 or biologically active fragment thereof.

The claimed invention encompasses inhibiting any Il-1 induced biological response in any mammal. However, IL-1 has functions other than in inflammation. Huleihel et al. teaches that IL-1 activity has been shown to be present in extracts of rat spermatozoa and in the rete testis fluid {Huleihel et al. (2004) Asian J. Androl 6:259-268; Section 3.1}. Further, Huleihel et al. teaches that IL-1 is able to modulate Sertoli cell functions. IL-1 has been shown to affect various testicular functions such as stimulation of germ cells (Section 3.1.1) Finally Huleihel et al. states that spermatogenesis is a process which is regulated by endocrine and autocrine/paracrine factors, such as IL-1 (Section 4). The specification does not disclose how inhibiting IL-1 related spermatogenesis accomplishes the stated utility of treating connective tissue diseases (Specification pg. 10).

The specification does not disclose any specific IL-10 polynucleotide sequence or fragment thereof to be used in a method of inhibiting an IL-1 induced biological response in a mammal. The specification only discloses the prospective use of a nucleic acid sequence encoding any IL-10 or a biologically active fragment thereof (pg. 26, lines 17-22). None of the working examples disclose any results from experiments actually performed. However, the specification does not provide any guidance on the nucleic acid sequence, or protein structure of IL-10 from any species and what motifs or domains must be conserved in order to retain function and inhibit IL-1 activity. The term polynucleotide sequence broadly encompasses any cDNA, RNA or genomic DNA

sequence encoding IL-10 from any species. For example, the mouse IL-10 genomic sequence has five exons, four introns, and is 5.1 kb long {Kim et al. (1992) J. Immunol. 148:3618-3623}. Generally, when expressing a gene in cells for gene therapy the cDNA is used since the appropriate splicing of the exons is already accomplished {Sandall L.J. (2000) Clinical Orthopaedics and Related Research 379S:S9-S16; pg. S12, Col.2, pgph 1}. The specification does not provide any guidance that a polynucleotide encoding a full-length IL-10 genomic DNA sequence from any species can be used to inhibit any IL-1 induced biological response. Finally the specification fails to provide guidance on the administration of any naked RNA's to any mammal in order to inhibit an IL-1 induced biological response in a mammal.

Further, while the specification contemplates using any viral or non-viral vectors to deliver the nucleic acid encoding IL-10 or biologically active fragments thereof, the specification does not provide any guidance on any regulatory elements to be operably linked to the IL-10 sequence, such as a promoter, kozak sequence, or poly A site. Further the specification does not specify whether the IL-10 polynucleotide sequence is to be constitutively expressed or under the control of an inducible promoter. Finally, the specification does not provide any information on the routes of administration of the IL-10 nucleic acid. In the related field of DNA based vaccines, the route of delivery is known to have a significant effect on the efficiency of expression. McCluskie et al. teaches that the route of delivery of DNA vaccine influences immune responses in laboratory animals {McCluskie et al. (1999) Mol. Med. 5:287-300; Abstract}. Specifically, in one study McCluskie et al. only observed antibody responses to injected routes of administration of DNA vaccines and not to non-injected injected routes of

administration of DNA vaccines, such as oral routes, sub lingual, inhalation and vaginal wall because of variation in transfection efficiency (Abstract). Further, the specification does not provide any evidence demonstrating that an IL-1 induced biological response can be inhibited in the joint of any mammal through a method of gene therapy using any polynucleotide that encodes any IL-10 cytokine or biologically active fragment thereof, administered by any route. All of the working examples disclosed in the specification, in regards to administration of any polynucleotide that encodes any IL-10 cytokine or biologically active fragment thereof, are prospective.

Verma et al. states that, the Achilles heel of gene therapy is gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, col. 3, pgph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems are entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-

viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trail and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Finally, Verma et al. teaches that the *in vivo* approach of gene therapy is unpredictable because of an inability to deliver genes efficiently and to obtain sustained expression (see page 239, 3rd column, line 10). "Although more than 200 clinical [gene therapy] trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (page 239, column 1, line 16).

The claims encompass a method of *ex vivo* gene therapy using any polynucleotide that encodes any IL-10 cytokine or biologically active fragment thereof. However, the combination of vector, promoter, level of expression, target tissue, dosage and route of administration required to obtain a therapeutic effect using *ex vivo* gene therapy were unpredictable at the time of filing. For example, Ross et al. teaches an *ex vivo* gene therapy approach used to treat melanoma tumors (Sept. 10, 1996, Human Gene Therapy, Vol. 7, page 1781-1790). It resulted in only one melanoma patient who might be considered to have had a clinical response, however it may have occurred spontaneously because melanoma is known to regress spontaneously (page 1786, column 1, paragraph 2). Ross et al. concludes that it is unpredictable whether a therapeutic result can be obtained using *ex vivo* gene therapy (page 1786, column 1, paragraph 2). The specification does not provide any working examples or guidance on the combination of vector, promoter, level of expression, target tissue, dosage and route of administration of the cells transfects with any polynucleotide that encodes any IL-10 cytokine or

biologically active fragment thereof.

Given the lack of guidance in the specification on administration to any mammal of any specific polynucleotide that encodes any IL-10 cytokine or biologically active fragment thereof, the lack of guidance on any route of administration of said polynucleotide, the lack of guidance on the nature of the IL-10 polynucleotide, such as the species, sequence and structure, the lack of guidance on the use of any specific viral vector, the lack of guidance on an *ex vivo* method administration of any cell comprising any polynucleotide that encodes any IL-10 cytokine or biologically active fragment thereof, the lack of guidance that any route of administration of any polynucleotide that encodes any IL-10 cytokine or biologically active fragment thereof can inhibit an IL-1 induced biological response in a joint, and the teachings in the art on the unpredictability of a method of gene therapy without validating the polynucleotide to be used, the skilled practitioner would be unable to practice the claimed invention without extensive and undue experimentation.

No claims allowed.

Examiners comment

Please note that the closest prior art of record is exemplified by US Patent NO. 5,858,355 (1999) which contemplates a method of inhibiting an IL-1 induced biological response with a polynucleotide encoding IL-10 or a biologically active fragment thereof.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr.

Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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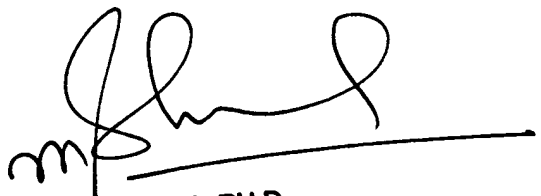

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